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ORIGINAL ARTICLE
Atrial fibrillation

Sodium-glucose cotransporter-2 inhibitors and the risk of atrial fibrillation in patients with type 2 diabetes: a population-based cohort study

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Aims Sodium-glucose cotransporter-2 inhibitors (SGLT-2is) have a direct cardiac effect that is likely to be independent of its glucose lowering renal effect. Previous research has shown that SGLT2-is mitigate heart failure and prevent arrhythmic cardiac death. Our objective is to determine whether SGLT-2is reduce atrial fibrillation (AF) in comparison to other second-to third-line antidiabetic drugs in type 2 diabetes.

Methods and results We conducted a population-based, new-user active comparator cohort study using data from the UK Clinical Practice Research Datalink. We identified a cohort of patients initiating a new antidiabetic drug class between January 2013 and September 2020. This cohort included patients initiating their first ever non-insulin antidiabetic drug, as well as those who switched to or added-on an antidiabetic drug class not previously used in their treatment history. Individuals with a diagnosis of AF or atrial flutter at any time before cohort entry were excluded. Cox regression analysis with time-dependent covariates was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) of AF comparing SGLT-2-is with other second-line to third-line antidiabetic drugs. Stratified analyses were performed according to sex, diabetes duration (<5 or ≥ 5 years), body mass index (BMI), HbA1c, and presence of heart failure.

The cohort comprised 142 447 patients. SGLT-2is were associated with a statistically significant reduced hazard of AF compared to other second-line to third-line antidiabetic drugs (adjusted HR: 0.77 [95% CI: 0.68–0.88]). This reduced risk was present in both sexes but was more prominently among women (adjusted HR_{women}: 0.60 [95% CI: 0.45–0.79]; HR_{men}: 0.85 [95% CI: 0.73–0.98]; *P*-value interaction: 0.012). There was no evidence for effect modification when stratifying on duration of diabetes, BMI, HbA1c, or presence of heart failure.

Conclusion SGLT-2is were associated with a reduced risk of AF in patients with type 2 diabetes compared to other second-line to third-line antidiabetic drugs. This reduced risk occurs in both sexes but more prominently among women.

Keywords SGLT-2 inhibitors • Diabetes mellitus • Atrial fibrillation • Pharmacoepidemiology

Introduction

Type 2 diabetes is associated with an increased risk of all-cause mortality,[1,2] and previous research has reported an increased incidence of atrial fibrillation (AF) in patients with diabetes.[3] Sodium-glucose cotransporter-2 inhibitors (SGLT-2is) are used to improve glycaemic control in type 2 diabetes and exert their therapeutic action by reducing glucose and sodium reabsorption via inhibition of the SGLT-2 in the proximal tubule of the kidney.[4] Accumulating evidence indicates that SGLT-2is have a direct cardiac effect that is likely to be independent of its glucose lowering renal effect.[5–8] For instance, reduced risk of sudden cardiac arrest or sudden death associated with SGLT-2is has been reported.[9–12] We have previously reported that SGLT-2is were associated with a lower risk of sudden cardiac arrest when compared to glucagon-like peptide-1 receptor agonists (GLP-1 RAs)[9] or to other second-line to third-line antidiabetic

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drugs,[10] although the latter association failed to reach statistical significance due to small number of sudden cardiac arrest events.[10] Our previous findings have been supported by other studies as well.[11,12] Several (off-target) actions that have been described include favourable effects on the cytosolic Na^+ and Ca^{2+} homeostasis by impairing of the myocardial Na^+/H^+ exchanger and of the cardiac late sodium current, improving mitochondrial function, reduction of free radicals and reducing inflammation,[5–8,13] which all have been shown to contribute to the genesis of AF.[5,6] We therefore hypothesized that by favourably interfering with Na^+ and Ca^{2+} homeostasis, inflammation, the late sodium current, and/or free radical generation, SGLT-2is reduce the risk of AF in patients with diabetes. A better understanding regarding the AF reducing potential of SGLT-2is may guide a more informed choice of antidiabetic therapy in type 2 diabetes. Accordingly, we sought to investigate whether the use of SGLT-2is was associated with a reduced risk of AF in patients with type 2 diabetes when compared with the use of other second-line to third-line antidiabetic drugs in a population-based cohort study.

Methods

Data sources

Data were obtained from the Clinical Practice Research Datalink (CPRD) GOLD, which is a large, computerized database of longitudinal primary care records comprising more than 11 million patients; these have been shown to be representative of the general population in the UK.[14] The CPRD contains information on all medical diagnoses and procedures, laboratory values, lifestyle characteristics, and all the prescriptions issued at the practice.[14] The data collected in the CPRD have been shown to be of high quality and validity, since data quality is monitored at the practice and patient level and practices contribute to the CPRD only when their data quality is up to research standards.[14] The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 20_000197). Patient informed consent was not necessary since the data were anonymized for research purposes.

Study cohort

We identified a cohort of patients initiating a new antidiabetic drug class between January 2013 (the year in which the first SGLT-2i entered the market in UK) and September 2020. This cohort included patients initiating their first ever non-insulin antidiabetic drug, as well as those who switched to or added-on an antidiabetic drug class not previously used in their treatment history. Cohort entry was defined by the date of this new prescription. We excluded individuals with a diagnosis of AF or atrial flutter at any time before cohort entry, those with <6 months of valid medical history in the CPRD before the cohort entry date, those who received insulin as their first antidiabetic drugs because such patients are likely to have type 1 diabetes or advanced type 2 diabetes, and women with polycystic ovarian syndrome and gestational diabetes at baseline, as these are indications for metformin therapy.

All patients meeting the study inclusion criteria were followed from cohort entry until the event of interest (AF/atrial flutter), death, the end of registration with the general practice, or end of the study period (September 2020), whichever occurred first. This study approach has been previously used by this research group.[10]

Exposure

We defined exposure in a time-varying manner, where each person-day at any time during the follow-up was classified into one of the following three categories: (1) SGLT-2i users (e.g. alone or in combination with other antidiabetic drugs), (2) users of other second-line to third-line antidiabetics (defined as initiation of treatment with either thiazolidinediones, DPP-4 inhibitors, alpha-glucosidase inhibitors, GLP-1 analogues, prandial glucose regulators, combination of antidiabetic drugs, or switch to or add-on of an antidiabetic drugs, including insulin), and (3) users of metformin or sulfonylureas in monotherapy as these are prescribed as first-line drugs. For all exposure categories, exposed person-time was defined by the prescription duration plus a 30-day permissible gap period, to allow for irregular use. This exposure definition has been previously used[10] and is described in detail elsewhere.[15]

Covariates

We defined the following confounders as time-dependent variables at the start of each time interval: age, ischaemic heart disease including myocardial infarction, heart failure, peripheral artery disease, the presence of an implantable cardioverter defibrillator (ICD) or pacemaker, hypertension, and stroke. In addition, we assessed smoking status (current, recent, and past), body mass index (<30, ≥30 kg/m^2), kidney function (estimated glomerular filtration rate (eGFR) in mL/min) and haemoglobin A1c (HbA1c) level (≤7.0, 7.0–8.0, >8) by using the most recent values at the start of each time interval. Finally, we assessed the number of cardiovascular drugs being prescribed (0, 1, 2, ≥ 3) as a time-dependent variable 6 months prior to the start of each time interval.

Statistical analyses

Cox regression analysis was used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) of AF, comparing use of SGLT-2is with use of other second-line to third-line antidiabetics. The models were adjusted for the following confounders: age, sex, ischaemic heart disease (including acute myocardial infarction), heart failure, peripheral artery disease, hypertension, stroke, duration of diabetes, smoking, HbA1c, body mass index, kidney function, the presence of ICD/pacemaker, and number of cardiovascular drugs. We further investigated the relation between SGLT-2is and AF by stratifying according to sex, diabetes duration (<5 or ≥5 years), body mass index (<30 or ≥30), HbA1c (≤8 or >8), and the presence of cardiovascular disease including heart failure. The presence of interaction on a multiplicative scale between SGLT-2is and these variables was estimated by consecutively including the cross-product of the two factors as a variable in the model. A two-tailed *P*-value of <0.05 was considered indicative of a significant difference among groups. Finally, three prespecified sensitivity analyses were conducted to assess the robustness of the results. First, the primary analysis was repeated after by not allowing concomitant use of insulin (a marker of advanced diabetes) during follow-up. Second, the primary analysis was repeated using alternative comparator consisting of use of dipeptidyl peptidase-4 (DPP-4) inhibitors. Third, the primary analysis was repeated using a reference category without users of only concomitant metformin and sulfonylurea drugs, as these patients may be considered as having less advanced diabetes. Fourth, the primary analysis was repeated by excluding patients with stroke and/or anticoagulant use.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the entire cohort stratified by antidiabetic drug use at cohort entry. The study population consisted of 142 447 new users of antidiabetic drugs, with 14 409 SGLT-2i users, 43 620 other second-line to third-line antidiabetic drug users, and 84 418 first-line antidiabetic drug users at cohort entry (characteristics of first-line antidiabetic users are not included in *Table 1*). Compared with other second-line to third-line antidiabetic users, SGLT-2i users were younger (61 vs. 65 years), more likely to be obese (74% vs 55%), had higher HbA1c levels (>8.0: 80% vs 67%), and a longer duration of diabetes (10.6 vs 8.0 years). Also, SGLT-2i users had a higher prevalence of insulin use (23% vs 6%), while the prevalence of cardiovascular comorbidities was in general lower compared with users of other second-line to third-line antidiabetic users. Users of SGLT-2is were similar to users of other second-line to third-line antidiabetic users with respect to sex, smoking status, and the number of cardiovascular drug prescriptions used.

Table 1 Baseline characteristics of users of sodium-glucose cotransporter-2 inhibitors and other second-line to third-line drugs

	Sodium-glucose cotransporter-2 inhibitors (n = 14 409)	Other second-line to third-line drugs (n = 43 620)
Age in years, mean (SD)	60.50 (9.93)	64.97 (12.63)
Male, n (%)	8799 (61.1)	26 016 (59.6)
Smoking status, n (%)		
Current	2558 (17.8)	8058 (18.5)
Past	7221 (50.1)	21 279 (48.8)
Never	4615 (32.0)	14 194 (32.5)
Unknown	15 (0.1)	89 (0.2)
BMI in kg/m^2, n (%)		
<30	3763 (26.1)	19 099 (43.8)
≥30	10 604 (73.6)	24 153 (55.4)
Unknown	42 (0.3)	368 (0.8)
Haemoglobin A_{1c} level, n (%)		
≤ 7.0	598 (4.2)	3639 (8.3)
7.1–8.0	2168 (15.0)	9531 (21.9)
>8.0	11 562 (80.2)	29 409 (67.4)
Unknown	81 (0.6)	1041 (2.4)
eGFR in mL/min, n (%)		
>90	6943 (48.2)	16 596 (38.2)
60–90	6736 (46.7)	17 923 (41.1)
45–60	577 (4.0)	4623 (10.6)
30–45	93 (0.6)	2989 (6.9)
15–30	11 (0.1)	927 (2.1)
<15	0	101 (0.2)
Unknown	49 (0.3)	461 (1.1)
Duration of diabetes in years, mean (SD)	10.6 (5.0)	8.0 (5.3)
Comorbidities, n (%)		
Ischaemic heart disease including myocardial infarction	2142 (14.9)	7398 (17.0)
Heart failure	337 (2.3)	1490 (3.4)
Periphery arterial disease	385 (2.7)	1508 (3.5)
ICD/pacemaker	92 (0.6)	519 (1.2)
Hypertension	8629 (59.9)	25 880 (59.3)
Stroke	754 (5.2)	3393 (7.8)
Pharmacotherapy, n (%)		
Beta-blockers	3172 (22.0)	10 167 (23.3)
Calcium channel blockers	4313 (29.9)	12 991 (29.8)
Diuretics	3399 (23.6)	11 895 (27.3)
Renin-angiotensin system inhibitors	9709 (67.4)	26 145 (59.9)
Statins	11 369 (78.9)	32 654 (74.9)
Nitrates	910 (6.3)	3168 (7.3)
Antiarrhythmic drugs	11 (0.1)	75 (0.2)
Anticoagulantia	212 (1.5)	897 (2.1)
Cardiovascular drugs, n (%)		
0	1247 (8.7)	5055 (11.6)
1	3017 (20.9)	9216 (21.1)
2	3995 (27.7)	10 833 (24.8)
≥3	6150 (42.7)	18 516 (42.4)
Concomitant antidiabetic drug use		
Metformin	12 326 (85.5)	36 990 (84.8)
Sulfonylureas	8858 (61.5)	28 864 (66.2)
Thiazolidinediones	1262 (8.8)	4346 (10.0)
GLP-1 analogues	22 (0.2)	227 (0.5)
DPP-4 inhibitors	3794 (26.3)	28 939 (66.3)
SGLT-2 inhibitors	14 409 (100.0)	0
Insulin	3237 (22.5)	2784 (6.4)
Others	73 (0.5)	505 (1.2)

Association between SGLT-2is and AF

Table 2 presents the results on the incidence of AF. Users of SGLT-2is had a lower incidence rate of AF compared with users of other second-line to third-line antidiabetic drugs (*Table 2*). After adjusting for all the confounders, use of SGLT-2is was statistically significant associated with a reduced hazard of AF compared with users of other second-to third-line antidiabetic drugs (HR 0.77, 95% CI 0.68–0.88, *Table 2*). Stratification according to sex showed that this reduced risk was present in both sexes but was more prominently among women (HR_{women} 0.60, 95% CI 0.45–0.79; HR_{men} 0.85, 95% CI 0.73–0.98); *P*-value interaction: 0.012, *Figure 1*). There was no evidence for effect modification when stratifying on duration of diabetes, body mass index, HbA1c or presence of cardiovascular disease including heart failure (*Figure 1*). Finally, our sensitivity analyses yielded consistent findings, as HRs did not vary when analyses were conducted by taking a reference category without users of concomitant metformin and sulfonylurea drugs only (HR 0.75, 95% CI 0.65–0.85), when DPP-4 inhibitors served as the reference group (HR 0.76, 95% CI 0.66–0.87), when we did not allow concomitant use of insulin (HR 0.75, 95% CI 0.65–0.87), or when we excluded patients with stroke and/or anticoagulant drug use (HR 0.73, 95% CI 0.63–0.84).

Discussion

In this population-based cohort study, we showed that SGLT-2i use was associated with a reduced risk of AF compared with other second-line to third-line antidiabetic drugs in type 2 diabetes. This reduced risk occurred in both sexes but was more prominent among women and appeared to be independent of diabetes duration, body mass index, HbA1c, and the presence of cardiovascular comorbidities including heart failure. Lastly, our finding of reduced AF risk with

Table 2 Association between the use of sodium-glucose cotransporter-2 inhibitors and the HR of AF

Exposure	Events, No.	Person-years	Incidence rate per 1,000 person-years (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Second-line to third-line antidiabetic drugs	1504	149,798	10.04 (9.54–10.56)	Reference	Reference
Sodium-glucose cotransporter-2 inhibitors	287	58,673	4.89 (4.36–5.49)	0.48 (0.42–0.54)	0.77 (0.68–0.88)

CI, confidence interval; HR, hazard ratio. Adjusted for age, sex, ischaemic heart disease (including acute myocardial infarction), heart failure, peripheral artery disease, hypertension, stroke, kidney function, duration of diabetes, smoking, HbA1C, body mass index, ICD/pacemaker, and number of cardiovascular drugs

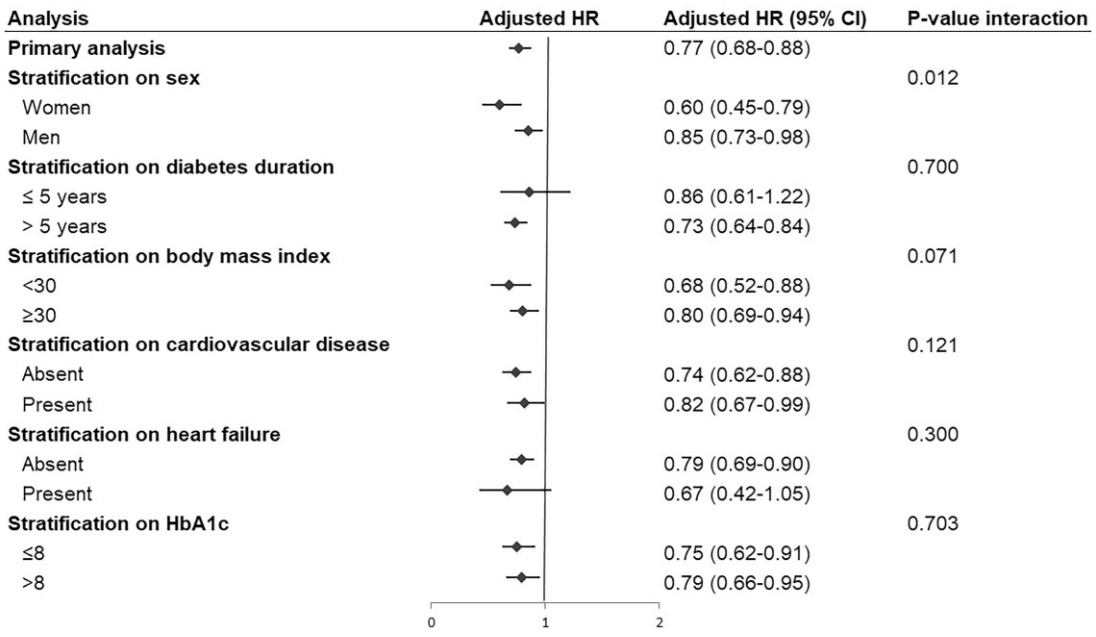

Figure 1 Results of primary analysis and stratified analysis, showing adjusted HRs and 95% CIs for association between use of sodium-glucose cotransporter-2 inhibitors and atrial fibrillation compared to other second-line to third-line antidiabetic drugs.

SGLT-2is remained consistent in subjects without concomitant use of insulin.

Previous studies have shown that diabetes is associated with multiple types of cardiovascular diseases,[16] including an increased risk of AF.[3] Consequently, confounding by disease duration (time-lag bias) may occur in our study if users of SGLT-2is have a shorter duration of diabetes compared to users of other second-line to third-line antidiabetic drugs; their comparison can induce confounding by disease duration, as a shorter duration of diabetes may be associated with lower AF incidence.[17] In our study, however, SGLT-2i users had a longer diabetes duration and a higher prevalence of insulin compared with users of other second-line to third-line antidiabetic drugs at cohort entry, making this notion unlikely. Nevertheless, despite being in a more advanced stage of diabetes than users of other second-line to third-line antidiabetic drugs, users of SGLT-2is still had a lower AF risk. Moreover, we found that the reduced AF risk of SGLT-2is occurred independent from diabetes duration. Further, we noticed that there was an imbalance in the use of DPP-4is between users of SGLT-2is or other second-line to third-line antidiabetic drugs at baseline (26.3% vs. 66.3%). A previous meta-analyses reported an increase in the risk for atrial flutter (but not for any other major cardiac arrhythmias) associated with DPP-4is,[18] while another study reported a lower AF risk associated with DPP-4is compared to other second-line antidiabetic drugs.[19] Accordingly, we performed a subgroup analyses in which we have excluded users of DPP-4is; our finding regarding lower AF risk associated with SGLT-2is did not change (adjusted HR 0.78, 95% CI 0.66–0.91). It seems therefore unlikely that such imbalance have impacted our results.

We found in our study that users of SGLT-2is generally had less cardiovascular comorbidities than users of other second-line to third-line antidiabetic drugs. Consequently, the more favourable cardiovascular risk profile of SGLT-2i users may have contributed to some extent to the reduced AF risk associated with SGLT-2i use in our study. However, use of SGLT-2is remained associated with reduced AF risk after adjustment for these variables in our multivariate model. Furthermore, our observation of reduced AF persisted in individuals without recorded diagnosis of cardiovascular comorbidities, suggesting that it is unlikely that patient differences alone explain this relationship.

Several mechanisms for our observed association of SGLT-2is with AF may be proposed. Previous research has shown that SGLT-2is mitigate heart failure in patients with diabetes.[20,21] Given that patients with heart failure tend to develop AF,[22] it could be that SGLT-2is have indirect protective effects on AF in patients with diabetes through its positive effect on heart failure. However, the association between SGLT-2is and reduced AF risk in our study persisted after adjustment for heart failure. Furthermore, our finding of reduced AF remained consistent when we performed analysis in individuals with the absence of heart failure. This observation suggests that it is unlikely that SGLT-2is reduce AF risk only through its positive effects on heart failure alone. Obesity appears to be another key risk factor for AF,[23] and therefore, the observed association between SGLT-2is and reduced AF could be related to the body weight reducing effects of SGLT-2is. In our study, body mass index was defined prior to start of antidiabetic drugs. As a consequence, it is not possible to estimate the effect on body mass index. Therefore, our study design does not exclude the possibility that body weight reduction at least in part may have explained the results.

Taking together, our data suggest a direct impact of SGLT-2is on AF. Several potential mechanisms could be speculated. Previous research demonstrated that SGLT-2is seemed to favourably interfere with the Na^+ and Ca^+ ion homeostasis by directly blocking the cardiac Na^+/H^+ exchanger (NHE), thereby decreasing the cytoplasmic Na^+ and Ca^{2+} concentrations ($[Na^+]_c$, $[Ca2^+]_c$) and increasing the mitochondrial Ca^{2+} concentration ($[Ca_{2+}]_m$) in cardiomyocytes.[24] Changes in Ca^{2+} concentrations are likely to occur secondary to the decreased $[Na^+]_c$ via the sarcolemmal and mitochondrial Na^+/Ca^{2+} exchanger (NCX).[5] Because diabetes may also result in intracellular Na^+ and Ca^{2+} loading,[25] inhibition of NHE by SGLT-2is may diminish the incidence of triggered activity that serves as the initiation of AF. However, it should be emphasized that more studies are needed to confirm these mechanisms. Additionally, SGLT-2is may decrease $[Ca^{2+}]_c$ by reducing the Ca^{2+}/calmodulin-dependent kinase II (CaMKII) activity.[6] CaMKII is an important regulator of Ca^{2+} handling which phosphorylates the ryanodine receptor 2 in atrial myocytes to exacerbate Ca^{2+} leak from the sarcoplasmic reticulum, thereby causing Ca^{2+} loading.[6] Since CaMKII is elevated in diabetes,[26] reducing CaMKII activity could therefore be another relevant mechanism by which SGLT-2is prevent Ca^{2+} overload and provide its AF reducing effects in type 2 diabetes. Finally, SGLT-2is may decrease $[Ca^{2+}]_c$ through inhibition of the late component of the sodium current (late-I_{Na}).[5,6,27] Increased late Na^+ current drives NCX in its reverse mode, thereby increasing the $[Ca^{2+}]_c$ that may contribute to the development of AF.[6] Because an induced late-I_{Na} may also occur in diabetes,[28] inhibition of the late-I_{Na} by SGLT-2is may also be relevant mechanism in the prevention of AF. Alternative mechanisms of the anti-arrhythmic effects of SGLT2is relate to the potential anti-inflammatory and anti-free radical generating effects.[5,6,13]

Finally, the results of our study indicate that the reduced AF risk associated with SGLT-2i use was greater in women than in men, fitting to the observation that women have a longer atrial action potential duration than men, and potentially benefit more from the AF reducing effects of SGLT-2is.[29]

Previous Studies

Our finding of reduced risk of AF associated with SGLT-2i use is supported by previous studies. Shao et al. showed that SGLT-2i can ameliorate electrical and structural remodelling of the atria, and prevent AF in a type 2 diabetes rat model.[30] A meta-analysis by Li et al. investigated the association of SGLT-2i treatment with arrhythmia in clinical trials of patients with heart failure, diabetes mellitus, and chronic kidney disease.[31] They showed that SGLT-2i treatment was associated with a lower risk of AF.[31] Using a cohort design, Ling et al. studied the risk of new-onset AF associated with the use of SGLT2i compared to DPP-4 inhibitor, and showed a reduced risk of AF with SGLT-2i use.[32] These findings were supported by a study by Zelniker et al. in which the effect of the SGLT2i dapagliflozin on the incidence and total number of AF and atrial flutter events was investigated.[33] That study reported reduced risk of AF and atrial flutter events with dapagliflozin treatment regardless of the patient's previous history of AF, in patients with type 2 diabetes.[33] Using a longitudinal observational database, Engstrom et al. confirmed that SGLT-2is were significantly associated with a reduced risk of new-onset AF compared with use of glucagon-like peptide 1 receptor agonist.[34] A cohort study by Zhou et al. investigated the association between SGLT-2i use and the risk of AF compared with initiation of a DPP-4 inhibitor or a glucagonlike peptide-1 receptor agonist among older adults (age $\geq$ 66 years) with type 2 diabetes and showed that SGLT-2i use was associated with a reduced risk of incident AF.[35] Lee et al. compared the effects of SGLT-2is and DPP-4is on several adverse outcomes (i.e. new-onset ischaemic stroke/transient ischaemic attack, new-onset AF, all-cause and cardiovascular mortality) using a retrospective population-based cohort of type 2 diabetes mellitus and reported that SGLT-2i use was associated with lower risk of incident AF, stroke/transient ischaemic attack, cardiovascular and all-cause mortality outcomes compared to DPP-4is use after propensity score matching.[36] Finally, Lui et al. compared the risk of incident AF between SGLT-2is and GLP-1 RAs by using a population-based, retrospective cohort of patients with type 2 diabetes.[37] In that study, a lower risk of incident AF associated with SGLT-2is was reported after propensity score matching.[37] It should be noted, however, that in the referenced observational studies information lacked on lifestyle cardiovascular risk factors such as smoking.[36,37] Moreover, in these studies post-baseline confounding may still be present despite propensity-matching. However, despite using a different data source, a different approach for adjusting confounders (propensity-score) and a different comparator group (DPP-4is, GLP-1 RAs), our finding of reduced AF risk associated with SGLT-2is was supported by these earlier studies.

Strengths and Limitations

This study has several strengths. A strength of the present study is its population-based design, in which large number of users of SGLT-2is was obtained, thereby rendering our findings representative for the community at large. Another strength is our new-user study design, which eliminated biases common in pharmacoepidemiologic studies.[17] Finally, to minimize possible confounding by indication, we used an active comparator design in which SGLT-2is were compared with other second-line to third-line antidiabetic drugs. Nevertheless, certain limitations of this study are worth considering. Drug information in the CPRD represents prescriptions, and thus misclassification of exposure may have occurred if these prescriptions were not filled or used by patients. However, such possible misclassification is expected to be non-differential between the exposure groups. Misclassification of exposure may also have occurred if patients were treated by medical specialists, because the prescription would not be recorded. However, since the management of type 2 diabetes in the UK occurs almost entirely through the primary care, a possible misclassification arising from this is expected to be minimal in our study. Further, underreporting of AF, and thereby misclassification of the outcome, may have occurred if AF was diagnosed by specialist and not recorded in the primary care. We expect that underreporting of AF would be non-differential between users of SGLT-2is and other second-line to third-line antidiabetics. Second, although we have adjusted for all the relevant cardiovascular comorbidities, we cannot rule out the

possibility of residual confounding from unmeasured or unknown variables. We attempted to reduce the impact of residual confounding using an active comparator and by performing several sensitivity analyses and by controlling for a wide range of potential confounders. Our main results were confirmed in these sensitivity analyses. However, it is still possible that residual confounders might have affected our observed associations given the observational nature of this study. A propensity-matched analysis could have strengthened our results, but it was not possible because of our time-dependent study design. On the other hand, propensity-matching does not take the changes of medical status (e.g. new diagnosis of comorbidities, discontinuation/add-on of co-medication) during the follow-up period into consideration which could lead to post-baseline confounding despite propensity-matching. Third, we noticed that users of SGLT-2is generally had less cardiovascular comorbidities (despite having a higher diabetes duration, body mass index, HbA1c) at baseline than users of other second-line to third-line antidiabetic drugs which could lead to limitations such as selection bias and confounding. However, our analyses in individuals without cardiovascular comorbidities provided additional support for the notion that our observed associations were due to SGLT-2i use. Moreover, our models were also adjusted for common risk factors of AF. Finally, our study design does not exclude the possibility that body weight reduction at least in part may have explained the results. Further studies are needed to identify the mechanisms of lower AF risk associated with SGLT-2is observed in our study.

Conclusion

Use of SGLT-2is is associated with reduced risk of AF in type 2 diabetes. This reduced risk occurred in both sexes but more prominently among women and appeared to be independent of diabetes duration, body mass index, HbA1c, and the presence of cardiovascular comorbidities including heart failure. Our findings may therefore help clinicians in tailoring antidiabetic drug therapy to minimize the risk of AF in patients with type 2 diabetes.

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Conflict of interest: None declared.

Data availability statement

This study is based on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. This study complied with all applicable laws regarding patient privacy. No direct patient contact or primary collection of individual patient data occurred; therefore, informed patient consent was not required. This study was approved by CPRD (protocol number 20_000197). Generic ethical approval for observational research approved by CPRD has been granted by a Health Research Authority Research Ethics Committee (East Midlands-Derby, UK; REC reference number 5/MRE04/87). Data sharing is not allowed under the licence agreement with CPRD. Data are available on request from CPRD; their provision requires the purchase of a license.

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